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EXAMINER	
KAM, CHIH MIN	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 03/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/508,095	ZUCHT ET AL.	
	Examiner	Art Unit	
	Chih-Min Kam	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *30-45* is/are pending in the application.

4a) Of the above claim(s) *35-39* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *30-34 and 40-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Status of the Claims

1. Claims 30-45 are pending.

Applicants' amendment filed December 12, 2003 is acknowledged, and applicants' response has been fully considered. Claims 3 and 18-29 have been cancelled, and new claims 30-45 have been added. Applicant has elected Group I, directed to the peptide and SEQ ID NO:22 for examination in Paper No. 11, and SEQ ID NOs: 17 and 19 have been included for examination in Paper No. 26. Claim 35 and 39 directed to the use of nucleic acid coding for the peptide and claims 36-38 directed to non-elected sequences are withdrawn from consideration. Thus, claims 30-34 and 40-45, and SEQ ID NOs:17, 19 and 22 are examined.

Objection Withdrawn

2. The previous objection of claims 18 and 19 is withdrawn in view of applicants' cancellation of the claim in the amendment filed December 12, 2003.

Claim Rejections - 35 USC § 112

3. The previous rejection of claims 18-29 under 35 U.S.C.112, first paragraph, is withdrawn in view of applicants' cancellation of the claim in the amendment filed December 12, 2003.

4. The previous rejection of claims 18, 24 and 29 under 35 U.S.C.112, second paragraph, is withdrawn in view of applicants' cancellation of the claim in the amendment filed December 12, 2003.

Claim Rejections - 35 USC § 102

5. The previous rejection of claims 18 and 28 under 35 U.S.C. 102(b) as being anticipated by Mukerji *et al.* (WO 98/08269), is withdrawn in view of applicants' cancellation of the claim, and applicants' response at pages 14-16 of the amendment filed December 12, 2003.

Informalities

The disclosure is objected to because of the following informalities:

6. The specification is objected to for "R_1, R_3 independently represents NH_2" and "R_2, R_4 independently represents COOH, $CONH_2$" (page 3) since each amino acid in the peptide (HN-CH(R)-CO) has already contained the amino (NH) and carbonyl (CO) groups. It is incorrect to cite "R_1, R_3 independently represents NH_2" for N-terminal end of the peptide, and "R_2, R_4 independently represents COOH, $CONH_2$" for C-terminal end of the peptide, it should be written as "R_1, R_3 independently represents H" and "R_2, R_4 independently represents OH, NH_2". Appropriate correction is required.

In response, applicants indicate "R_1, R_3" and "R_2, R_4" have been amended in the claim using H, or, OH or NH_2 as suggested by the Examiner (page 9 of the response), however, the term in the specification has not been corrected, thus objection remains.

Claim Objections

7. Claims 30-34 and 40-45 are objected to because the claim contains recitation of non-elected sequences such as SEQ ID NOs: 1-16, 20, 21, 23 and 24.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claim 34 is rejected under 35 U.S.C. 101 because the claimed recitation of a use, without setting forth any steps involved in the process, results in an improper definition of a process, i.e., results in a claim which is not a proper process claim under 35 U.S.C. 101. See for example *Ex parte Dunki*, 153 USPQ 678 (Bd.App. 1967) and *Clinical Products, Ltd.* v. *Brenner*, 255 F. Supp. 131, 149 USPQ 475 (D.D.C. 1966).

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 30, 32, 34 and 40-45 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a bifidogenic peptide with a defined sequence such as SEQ ID NO:17, 19 and 22, and a composition comprising the peptide, does not reasonably provide enablement for a peptide having bifidogenic properties and being a modified (e.g., amidated, acetylated, sulfated, phosphorylated, glycosylated, oxidized) derivative or fragment or fusion peptide of a specific bifidogenic peptide, a medicament or a composition containing the peptide, use of the peptide for preparing a medicament, and a method of promoting the growth of bifidobacteria or inhibiting the growth of non-bifidobacteria in the digestive tract by administering the peptide to an individual. The specification does not enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Claims 30, 32, 34 and 40-45 are directed to a peptide having bifidogenic properties and containing a specific sequence (e.g., SEQ ID NO:17, 19 or 22) or its modified (e.g., amidated, acetylated, sulfated, phosphorylated, glycosylated, oxidized) derivative or fragment or the combination of peptides, fragment and derivative by chemical bonding (claims 30, 40, 41), a medicament or a composition containing the peptide (claims 32, 44, 45), use of the peptide for preparing a medicament (claim 34), and a method of promoting the growth of bifidobacteria or inhibiting the growth of non-bifidobacteria in the digestive tract by administering the peptide to an individual (claims 42, 43). The specification, however, only discloses cursory conclusions (pages 1-14) without data supporting the findings, which state that peptides obtained from cow or human milk via a process of proteolytic cleavage and purification, or, their amidated, acetylated, sulfated, phosphorylated, glycosylated or oxidized derivatives or fragments thereof, would have bifidogenic properties (pages 1-2), and some sequences are listed as preferable embodiments (page 3). There are no indicia that the present application enables the full scope in view of bifidogenic peptides, the derivatives, fragments or fusion peptides thereof, and their use in the treatment as discussed in the stated rejection. The present application provides no indicia and no teaching/guidance as to how the full scope of the claims is enabled. The factors considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d at 731,737, 8 USPQ2d at 1400,1404 (Fed. Cir.1988)). The factors most relevant to this rejection are the breadth of the claims, the presence of working examples, the state of the prior art and

relative skill of those in the art, the unpredictability of the art, the nature of the art, the amount of direction or guidance presented, and the amount of experimentation necessary.

(1). The breadth of the claims:

The breadth of the claims is broad and encompasses unspecified variants regarding the derivatives, fragments or fusion peptides of the specific bifidogenic peptides, and their effects for in vivo treatment, which are not adequately described or demonstrated in the specification.

(2). The presence or absence of working examples:

The specification only demonstrates certain peptides such as SEQ ID NOs: 17 (casein K-63-117) and 19 (neutrophile lactoferrin 20-67), and the corresponding oxidation product exhibit bifidogenic activity (Example 1, page 8), the method of monitoring the growth-regulating activity on *E. coli* (Example 2), the method of monitoring the growth-regulating activity on *Bifidobacterium bifidum* (Example 3), and a formula to define bifidogenic activity (Example 4). There are no other working examples indicating the claimed variants or methods in association with the claimed invention.

(3). The state of the prior art and relative skill of those in the art:

The related art (Mukerji *et al.*, WO 98/08269) teach human kappa-casein having 182 amino acids comprises the peptide of SEQ ID NO:17; and Proulx et al. (Lait 74, 139-152 (1994)) indicate the casein hydrolysates produced by three proteolytic enzymes have bifidogenic activity. However, the general knowledge and level of the skill in the art do not supplement the omitted description, the specification needs to provide specific guidance on the identities of various modified derivatives, fragment or fusion peptides of the bifidogenic peptides; the treating conditions for promoting the growth of

bifidobacteria in individual using the specific peptide; and the effect of the peptide to be considered enabling for variants.

(4). The amount of direction or guidance presented and the quantity of experimentation necessary:

The claims are directed to peptides having bifidogenic properties and containing a specific sequence or its modified derivative or fragment or fusion peptide, use of the peptide for preparing a medicament, and a method of promoting the growth of bifidobacteria or inhibiting the growth of non-bifidobacteria in the digestive tract by administering the peptide. The specification indicates the peptides isolated and purified from cow milk or human milk can promote the growth of desired bacteria such as bifidobacteria more than that of other bacteria or by selectively inhibiting the undesired bacteria, which is defined as "bifidogenic" (page 3, first paragraph), and the peptide can be contained in medicaments or in food, and further asserts the peptides are suitable for treating diseases caused by various microorganisms (pages 4-5). The Example has only indicated the isolation and purification of certain peptides (SEQ ID Nos:17 and 19) which have bifidogenic properties (Example 1, page 8). However, the specification has not identified a specific modified derivative, fragment or fusion peptide having the bifidogenic property, nor has demonstrated the effects of various peptides in vivo treatment. There are no working examples indicating the bifidogenic activities of modified derivatives, fragments or fusion peptides of bifidogenic peptides. Furthermore, there is no *in vitro* or *in vivo* data indicating the bifidogenic peptide or the derivative, fragment or fusion peptide thereof is effective in promoting the growth of bifidobacteria or inhibiting the growth of non-bifidobacteria in individual. Since the specification does

not provide sufficient teachings, it is necessary to have additional guidance on the identities of various derivatives, fragments or fusion peptides of specific bifidogenic peptides, and the treating conditions such as dose of specific bifidogenic peptides for promoting the growth of bifidobacteria in individual, and to carry out further experimentation to assess the in vivo effect of bifidogenic peptides.

(5). Predictability or unpredictability of the art:

The claims encompass many peptide variants, but the treating conditions such as the dose for specific bifidogenic peptides and the effects of the peptides are not sufficiently described in the specification, the invention is highly unpredictable regarding the effects of various derivatives, fragments or fusion peptides of bifidogenic peptides.

(6). Nature of the Invention

The scope of the claims includes many structural variants, however the specification has not demonstrated the use and the effects of these peptide variants. Thus, the disclosure is not enabling for reasons discussed above.

In summary, the scope of the claim is broad, while the working example does not demonstrate the claimed variants and methods, the teaching in the specification is limited, and the effect of the claimed variant is unpredictable, therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the bifidogenic effect of the claimed variants.

In response, applicants indicate the rejection relies that the scope of the claims cover (1) disclosed embodiments not tested for bifidogenic activity and (2) non-disclosed variants of disclosed peptides, and the rejection fails to cite evidence to back up the allegations of non-enablement; satisfaction of the enablement does not require the

specification to contain even a single working example; regarding no identifed variants of the recited peptides, the statement of rejection fails to cite any evidence inconsistent with enablement; one skilled in the art would certainly possessed the knowledge needed in conjunction with the teachings of the instant application to readily effect the peptide variants modified by amidation, acetylation, sulfation, phosphorylation, glycosylation or oxidation such that the "bifidogenic propertites" of the non-modified peptide are retained; regarding testing which embodiments have bifidogenic activity, this does not involve undue experimentation; regarding the specification provides no treating conditions for promoting the growth of bifidobacteria in the individual, on the contrary, the treating condition (page 4, paragraph 4) has been described in the specification (pages 9-12 of the response). The response has been fully considered, however, the argument is found not persuasive because the claims encompass many structural variants regarding the modified derivatives of bifidogenic peptides and their use in the method of in vivo treatment, however, the specification does not provide sufficient teachings regarding the identities of peptide variants and their effects for in vivo treatment, the analysis of In re Wands factors (see the section above) provides the evidence that the undue experimentation is required. For example, the specification has not identified a specific modified derivative of the specific bifidogenic peptide, nor has demonstrated its bifidogenic property and its effect for in vivo treatment. Since the specification does not describe the structural characterization for bifidogenic activity of the peptides, it is necessary to have additional guidance on the identity of modified derivative and to carry out further experimentation to assess its bifidogenic activity and effect for in vivo treatment. Regarding the treating condition, a general dose range has been cited in the specification (page 4, paragraph 5),

however, there is no data indicating the dose for a specific bifidogenic peptide or its derivative is used in the treatment, nor demonstrating the treatment is effective.

10. Claims 30, 32, 34 and 40-45 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 30, 32, 34 and 40-45 are directed to a peptide having bifidogenic properties and containing a specific sequence (e.g., SEQ ID NO:17, 19 or 22) or its modified (e.g., amidated, acetylated, sulfated, phosphorylated, glycosylated, oxidized) derivative or fragment or the combination of peptides, fragment and derivative by chemical bonding (claims 30, 40, 41), a medicament or a composition containing the peptide (claims 32, 44 , 45), use of the peptide for preparing a medicament (claim 34), and a method of promoting the growth of bifidobacteria or inhibiting the growth of non-bifidobacteria in the digestive tract by administering the peptide (claims 42, 43). The specification indicates that peptides obtained from cow or human milk via a process of proteolytic cleavage and purification, or, their amidated, acetylated, sulfated, phosphorylated, glycosylated or oxidized derivatives or fragments thereof, would have bifidogenic properties (pages 1-2), and certain sequences are listed as preferable embodiments (page 3). The specification further asserts that SEQ ID NOs: 17 (casein K-63-117) and 19 (neutrophile lactoferrin 20-67), and the oxidation product exhibit bifidogenic activity (Example 1, page 8). However, the specification has not identified a specific modified derivative, fragment or fusion peptide of bifidogenic peptides, nor has shown the effects of these derivatives, fragments or fusion peptides in vitro or in vivo.

There is no example indicating the modified derivatives or fragments are functional. Without guidance on structure to function/activity, one skilled in the art would not know which region or residue(s) of the peptide is essential for function/activity, how to identify a functional peptide, and whether the modification on the amino acid residue would affect the bifidogenic property of the peptide. The lack of a structure to function/activity relationship and the lack of representative species for the modified derivatives, fragments or fusion peptides of the peptides having bifidogenic properties as encompassed by the claims, applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise terms that a skilled artisan would not recognize applicants were in possession of the claimed invention.

In response, applicants indicate the first paragraph of 112 contains no requirement for a structural disclosure, a description in functional terms can satisfy the enablement requirement; amidation, acetylation, sulfation, phosphorylation, glycosylation or oxidation of the recited peptides would effect a peptide structural modification readily apparent to one of ordinary skill in the art, and the fact the claims cover non-disclosed embodiments does not support the rejection; regarding the treatment of disease in accordance with the invention, applicants indicate the treating condition such as dose has been described in the specification, and it is not necessary to describe all embodiments in the specification, only one use in the specification needs be enabled to satisfy the requirement of 112, first paragraph (pages 12-14 of the response). The response has been fully considered, however, the argument is found not persuasive because the specification has not identified a specific modified derivative, fragment or fusion peptide of the specific bifidogenic peptide, nor has demonstrated bifidogenic property of the modified

derivative derivative, fragment or fusion peptide; regarding the treatment, a general dose range has been cited in the specification (page 5, paragraph 5), however, there is no in vitro or in vivo data indicating a specific peptide, its derivative or fragment within this dose range is effective in the treatment. Furhtermore, the function of the peptide depends on its structure, without identification of the structure of the peptide, and providing the correlation of structure to function/activity and representative species, one skilled in the art would not know how to identify a functional peptide. The claims encompass many structural variants, however, the teachings regarding the identities, the use and the effects of peptide variants are not described in the specification as indicated in the section above. Therefore, it is necessary to have additional guidance and to carry out further experimentation to assess the effect of modified derivative, fragment or fusion peptide of a specific bifidogenic peptide in the in vivo treatment.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

11. Claims 30-34 and 40-45 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

12. Claim 34 provides for the use of peptides for preparing a medicament for the treatment of diseases by misplaced microbial colonization, but, since the claim does not set forth any steps involved in the method/process, it is unclear what method/process applicant is intending to encompass. A claim is indefinite where it merely recites a use

without any active, positive steps delimiting how this use is actually practiced. Claim 34 is also indefinite because of the phrases "for example" and "such as", the cited phrases render the claim indefinite because it is unclear whether the limitation(s) following the phrase are part of the claimed invention. See MPEP § 2173.05(d). Claim 34 is also indefinite as to "deviations in the oral……, caries", it is not clear how much deviation in the oral, intestinal and vaginal floras, caries would turn to a disease state. A misspelled word "microbially6" is cited at line 4 of claim 34.

13. Claims 30-34, 41, 43 and 45 are indefinite because of the use of the term "amidated, acetylated, sulfated, phosphorylated, glycosylated, oxidized derivatives and fragments, thereof" or "by the combination of the peptides, fragments and derivatives by chemical bonding". The cited term renders the claim indefinite, it is unclear what amino acid sequence is amidated, acetylated, sulfated, phosphorylated, glycosylated and oxidized as to "thereof", and what parent peptide is referred to as to "fragments thereof"; and what amino acid sequence is obtained as to combining the peptides, fragments or derivatives by chemical bonding. Claims 31-34, 43 and 45 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

14. Claim 40 is indefinite for using the terms "R_1, R_3 independently represent NH_2" and "R_2, R_4 independently represent COOH, $CONH_2$". It is not clear what groups the N- and C-terminal ends of the peptide have since each amino acid (HN-CH(R)-CO) in the peptide has already contained the amino (NH) and carbonyl (CO) groups. Claim 40 is also indefinite as to "amino acid sequence 1-62 of human κ-casein", it is not clear whether "1-62 of human k-casein" refers to amino acid residues 1-62 of κ-casein, if it is,

a "SEQ ID NO:" should be cited in the claim. Claims 42 and 44 are included in the rejection because they are dependent on rejected claims and do not correct the deficiency of the claim from which they depend.

In response, applicants indicate "R_1, R_3" and "R_2, R_4" have used the term (H, or, OH or NH_2) as suggested by the Examiner (page 9 of the response), however, claim 40 still contains the uncorrected form, thus rejectiion remains.

Conclusion

15. No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chih-Min Kam whose telephone number is (571) 272-0948. The examiner can normally be reached on 8.00-4:30, Mon-Fri.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571) 272-0951. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 308-4227 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Chih-Min Kam, Ph. D. CMK
Patent Examiner

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March 11, 2004

ROBERT A. WAX
PRIMARY EXAMINER